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09/744,679	04/11/2001	RACHEL BAR-SHAVIT	108366	3009

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Oliff & Berridge
PO Box 19928
Alexandria, VA 22320

EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,679	BAR-SHAVIT, RACHEL	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2003 and Interview 9-15-2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 5, 6, 9-11, 14-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 6, 9-11, 14-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,10,19* .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

The objection to the specification set forth in the prior Office action, mailed 12-23-2002 is withdrawn in response to the Abstract filed 06-23-2003.

The objection to the specification set forth in the prior Office action mailed 12-23-2003 for failing to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 has been withdrawn in response to the Interview conducted 09-15-2003, wherein the examiner agreed to add sequence identifiers by informal Examiner's amendment to reflect the changes Applicant submitted in the amendment filed August 29, 2001, which could not be entered. These changes were made by informal Examiner's amendment because the underlining present in the originally filed specification made it difficult to conform to the current amendment practice. These amendments, in concert with the changes made to Figure 10, place the Application into compliance with the sequence rules.

Claim Objections

The objections to claims 4, 6 and 16, set forth in the prior Office action, mailed 12-23-2002 are withdrawn in response to Applicant's amendments filed 06-23-2003.

Drawings

The replacement drawing for Figure 10 was received on August 29, 2001. These drawings are acceptable.

Claim Rejections - 35 USC § 112

The rejection of record of claims 1, 2, 4-6, 9-12, and 14-19 under 35 U.S.C. 112, second paragraph set forth in the prior Office action, mailed 12-23-2002 are withdrawn in response to Applicant's amendments filed 06-23-2003, however, new rejections, in response to Applicant's amendments, are set forth herein.

The following is a quotation of the second paragraph of 35U.S.C 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is indefinite due to the recitation "being". It is unclear what the scope of "being" is with respect to the claimed antisense sequence, for example, whether this is meant to be closed or open language. The skilled artisan could not determine whether the claimed antisense comprises or consists of SEQ ID NO:7.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 6, 10, 11 and 14-19 are maintained as rejected and newly submitted claims 21-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention, for the reasons of record set forth in the prior Office action (mailed 12-23-2002) and are set forth herein to reflect the amendments filed 06-23-2003.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1, 5, 6, 10, 11,14-19 and 21-26 are drawn broadly to methods of treating any type of metastatic tumor cell in a subject *in vivo* (whole organism) using an antisense molecule targeted to a thrombin receptor, methods of treating any disorder involving the implantation of a placenta in a female patient using an antisense molecule targeted to a thrombin receptor, including a vector expressed antisense molecule, and pharmaceutical compositions comprising an antisense molecule targeted to a thrombin receptor, including vectors which express an antisense molecule.

The specification provides examples wherein a vector expressing an antisense cDNA of thrombin receptor was transfected into one metastatic breast cancer cell line and the cells showed a reduction in invasion in a matrigel assay. The specification does not demonstrate any correlation with the inhibition of cell invasion in cell culture and a reduction of metastasis in vivo in a subject. The specification demonstrates that there is a temporal pattern of thrombin receptor mRNA expression in placental biopsies. The

specification does not provide any examples wherein a disorder involving placental implantation is treated, nor wherein antisense targeted to thrombin receptor is used to modulate the expression of thrombin receptor in placental tissue in vivo or in vitro or wherein an antisense molecule expressed from a vector is used in such methods. The specification does not present any examples wherein antisense targeted to thrombin receptor was delivered to metastatic cancer cells or placental cells *in vivo* (whole organism), nor wherein antisense targeted to thrombin receptor inhibited the expression of thrombin receptor mRNA in cells *in vivo* (whole organism), including antisense expressed from a vector. The specification does not provide any examples wherein treatment effects were obtained for metastatic tumor cells or a disorder involving the implantation of a placenta in a female subject. The specification has not provided any antisense composition or vector expressing an antisense molecule that has pharmaceutical treatment effects, since these compositions are claimed as pharmaceutical compositions and would, therefore, require pharmaceutical properties, these claims have been included in this rejection.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for

unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Gene therapy methods, wherein a vectors expresses an antisense molecule, encounter similar problems with accessibility and delivery and have additional unpredictable factors associated by vector based gene therapy methods (see for example Anderson et al., Verma et al., which discuss the nature of unpredictability of gene therapy). Expression of vectors *in vivo*(whole organism) is unpredictable, often too low for therapeutic effects or unexpectedly turned off (see Verma et al., for example). Effective expression requires an appropriate promoter-enhancer

combination, "the search for such combinations is a case of trial and error for a given type of cell"(see Verma, for example, p 240). Gene therapy methods also have issues with the difficulty of delivery of an effective amount of the vector, as well as the potential for loss of expression or a potentially fatal immune response.

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed, or make an antisense composition with pharmaceutical properties. The specification provides examples wherein antisense is delivered to cells *in vitro* and the invasion of metastatic cells is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological

conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to thrombin receptor to generally any target metastatic cancer cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect or deliver antisense to placental cells in vivo in a female subject. It is unclear whether successful delivery of antisense to placental cells would even provide a therapeutic effect for disorders involving implantation of a placenta. The specification indicates that thrombin receptor expression in placental tissue is temporal, yet there is no guidance on what particular times to regulate expression with antisense to provide a therapeutic effect, or what degree of increase or decrease in expression is required. Although the specification provides a vague indication of when expression is increased or decreased in placental tissue which has been displaced from implantation, it is unclear whether antisense would also change thrombin receptor levels in the tissue of the female subject and how that would influence implantation.

In order to practice the invention claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a

concentration effective to result in inhibition of the expression of thrombin receptor to a level sufficient to result in a pharmaceutical effect or to inhibit the metastatic potential of a cell in vivo or to provide a treatment for a disorder involving the implantation of a placenta in a female subject. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo* and determine the temporal requirements of regulation of thrombin receptor in a placenta in vivo. Gene therapy methods would further require the determination of factors including how to effectively deliver a vector to the target cell, how to maintain expression at a level an for a duration effective to achieve the desired outcome, particular enhancer-promoter combinations effective for the target cell, and how to prevent an unpredictable and potentially fatal immune response. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of treatment using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods of treatment, including those wherein the antisense is expressed in a vector, for metastatic cancer and placental implantation and the lack of working examples or examples which correlate with the claimed methods,

one skilled in the art would not be able to practice the methods of claims 1, 5, 6, 10, 11,14-19, and 21-26 without undue trial and error experimentation.

Response to Arguments

Applicant's arguments filed 06-23-2003 have been fully considered but they are not persuasive. In response to the rejection of record of claims 1, 2, 4-6, 10-12 and 14-19, set forth in the prior Office action, mailed 12-23-2003, Applicant argues that the claimed methods and pharmaceutical compositions are enabled and have submitted a declaration under 35 USC 1.132 in support of this argument. These arguments have been considered to the extent that they read on the rejection of claims 1, 5, 6, 10, 11 and 14-26 under 35 USC 112, first paragraph set forth herein, but have not been found to be persuasive.

The declaration under 37 CFR 1.132 filed June 23, 2003 is insufficient to overcome the rejection of claims 1, 5, 6, 10, 11,14-19, and 21-26 based upon a lack of an enabling disclosure, as set forth in the last Office action and further recited herein because: The declaration is not directed to the scope of the claimed subject matter and does not present any evidence to support that the disclosure or the prior art provide the required guidance to overcome the art recognized hurdles to practicing antisense and gene therapy based treatments, in vivo, as set forth in the rejection of record. The references relied upon by Applicant to support their position are post filing references and do not reflect the state of the art at the time of filing.

In response to the rejection of record under 35 USC 112, first paragraph, set forth in the prior office action, mailed December 23, 2002, for lacking enablement,

Applicant argues that the declaration filed June 23, 2003 is sufficient to overcome the rejection of record because the claimed invention is directed to the expression of a cDNA in antisense orientation within an expression vector and that references cited in the declaration demonstrate that such methods are enabled without undue experimentation.

The declaration filed June 23, 2003 asserts that the claimed invention is directed to the expression of a cDNA in antisense orientation, not to the short oligonucleotides discussed in the references cited in the rejection of record, and therefore, the discussion of ODNs in the cited references is not relevant to the instant invention. Further, Applicant states that antisense therapeutics have matured and, therefore antisense therapies can be considered acceptable methods for treatment that do not require undue experimentation. In support of this assertion, Applicant cites four references which provide successful examples of antisense treatment for metastatic tumor cells, three of which were published in 2003, one of which was published in 2000. Applicant disagrees with the statement that cell culture examples are not predictive of in vivo efficacy because almost all biomedical research begins with tissue culture work and is accepted as a first step towards developing in vivo treatments. Applicant argues that the references cited against claim 9 are all cell culture experiments and therefore the examiner appears to accept these references as serious scientific papers.

These arguments, as presented in the declaration and in the comments in response to the prior Office action are not found to be persuasive because contrary to Applicant's assertion, the claims are not limited to an antisense cDNA expressed from a

vector, but would encompass generally any antisense molecule, including short oligonucleotides. Additionally, in response to Applicant's amendments, which direct the claims to antisense expressed from a vector, additional elements that add to the unpredictability of the claims directed to vectors have been pointed out in the rejection under 35 USC 112, first paragraph, set forth herein. Applicant not provided any evidence or guidance that demonstrates that the skilled artisan would have been able to overcome the art recognized hurdles and unpredictability in antisense methods and gene therapy methods, as presented in the rejection of record. The standard for enablement is the guidance, state of the art and predictability of the invention at the time of filing. The references cited by Applicant to support the predictability of antisense do not address the guidance, state of the art and predictability of the invention at the time of filing, because each of these references were published years after the filing date of the invention. The references cited by Applicant are not relevant to the invention at the time of filing. Further, a few unexpectedly successful examples of treatment effects do not change the predictability of all treatment methods. The references cited by applicant do not teach that even in 2000 or 2003 antisense methods of treatment are predictable, for example, see the passages of Jen et al. pointed out in the rejection of record. It is unclear how the examples cited by Applicant would provide guidance for the instantly claimed methods, which are directed to a different target mRNA, different target cells and different disorders than the cited references. Although culture methods are a first step towards developing in vivo methods, Applicant's statements appear to agree with the Examiner's position, as Applicant indicates further development is

required to go from cell culture to in vivo treatments. Given the art recognized unpredictability of antisense, this development would require undue experimentation and it is unpredictable that antisense that inhibits in cells in culture would provide an effective treatment effect in vivo. Applicant's remarks about the references cited against claim 9, as presented in the prior Office action, are irrelevant to the rejection under 112, first paragraph. As presented in the prior version of the claims, claim 9 was directed to generally an antisense composition and encompassed an antisense molecule used in any setting, including in cell culture, which was disclosed in the cited references.

Claim Rejections - 35 USC § 102

The Declaration under 37 CFR 1.132 filed June 23, 2003 is sufficient to overcome the rejection of claim 9 based upon Evan-Ram et al.

The rejection of record of claim 9 under 35 U.S.C. 102 as being anticipated by Even-Ram et al. is withdrawn in response to the Declaration filed June 23, 2003.

The rejection of record of claim 9 under 35 U.S.C. 102(b) as being anticipated by Chaikof et al. is withdrawn in response to Applicant's amendments filed June 23, 2003.

The rejection of record of claim 9 under 35 U.S.C. 102(b) as being anticipated by Mattson et al. is withdrawn in response to Applicant's amendments filed June 23, 2003.

The rejection of record of claim 9 under 35 U.S.C. 102(b) as being anticipated by Herbert et al. is withdrawn in response to Applicant's amendments filed June 23, 2003.

The rejection of record of claim 9 under 35 U.S.C. 102(b) as being anticipated by Schaeffer et al. is withdrawn in response to Applicant's amendments filed June 23, 2003.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Coughlin et al. (WO 92/14750).

Coughlin et al. disclose expression vectors which comprise nucleotides sequences consisting of between 250 and 600 base pairs that hybridize to an RNA sequence of a thrombin receptor. This sequence comprises SEQ ID NO:7. The nucleotides sequences disclosed by Coughlin et al. are not being used as antisense sequences, but meet all of the physical limitations of the claims and, therefore, are encompassed in the claims.

Therefore, Coughlin et al. anticipates claims 9 and 20.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
December 29, 2003

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER